

session 14 – biological treatments

139 NEW IMMUNOLOGIC TREATMENTS FOR LYMPHOMA

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Idiotypic vaccines [R1]

Since B cell lymphomas are the clonal proliferation of lymphocytes, the immunoglobulin they express is unique and it can be regarded as a tumor-specific antigen.

Phase I/II clinical trial of idiotype vaccines:

Immune response: Almost all phase I and II trials have demonstrated that Id-vaccination can induce both humoral and cellular anti-idiotype immune responses.

Clinical response: Several phase I/II clinical trials have documented clinical tumor regression after Id-vaccination for patients who had residual disease before vaccination.

Correlation between immune responses and clinical outcome: In a study of 136 patients treated with Id-vaccine the induction of a specific anti-Id antibody response (35% of patients) was associated with significantly prolonged progression-free survival (8.21 vs 3.38 years, $p=0.018$). More recently, we have shown that the generation of anti-Id antibody was an independent predictor for better overall survival. Other groups suggest that T-cell responses may also be important.

Phase III clinical trials of idiotype vaccines:

Three phase III clinical trials have been initiated (Biovest, Genitope, and Favril). Two of them have finished accrual and one of them has just announced its first data analysis (Genitope).

The Genitope trial showed no difference in the progression-free survival between the arm vaccinated with Id-KLH plus GM-CSF vs the control arm vaccinated with KLH plus GM-CSF. However, there was a highly significant difference in among the patients on the specific vaccine arm who mounted a positive immune response compared to those who did not make an immune response.

With recent improvements in vaccine production, based on cell-free protein expression it will become possible to produce a customized idiotype vaccine in a matter of weeks, rather than months. This will enable clinical trials in which patients can be vaccinated as a primary treatment.

Future directions:

1) Explore in vivo vaccines: Our group has investigated the efficacy of intratumoral injections of CpG in patients with B-cell lymphoma. CpG is a TLR-9 ligand which activates dendritic cells and induces antigen presentation. This trial has just finished accrual (15 patients) and some clinical responses have already been observed;

2) Increase the function of the final effector cells A pilot study of CTLA-4 blockade after failure of Id-vaccine has shown some clinical efficacy: a partial response in a follicular lymphoma patient and a mixed response in a mantle cell lymphoma. A phase II trial evaluating the effects of anti-CTLA4 antibody in a larger cohort of patients with follicular or mantle cell lymphoma is currently ongoing. Other types of T cell modulation that either deplete or inactivate regulatory T cells or increase effector T cells function may also be tested.

[R1] This chapter includes Phase I/II and III clinical trials so I'd rather call it "Id vaccine" rather than "Ig-Id" which is too restrictive.

140 RITUXIMAB AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY: A REPORT OF 35 CASES

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Background: Progressive multifocal leukoencephalopathy (PML) is a demyelinating disorder of the brain caused by the reactivation of latent JC polyoma virus. PML is associated with profound immunosuppression such as: HIV, stem cell transplantation (SCT), purine analog therapy, organ transplantation, or lymphoma. Rituximab (R) is a B-cell depleting, monoclonal antibody, linked to the reactivation of hepatitis B and other viruses. We evaluated the characteristics of patients who developed PML after exposure to R, including the results of T-cell studies, when available.

Methods: Data sources included clinical observations of the authors, reports from the FDA MedWatch database, medical literature cases, and reports from the manufacturer of R, Genentech, that were submitted to the United States Food and Drug Administration. Reports that did not confirm PML diagnosis or were associated with known HIV were excluded.

Results: Of 51 unique cases identified, 2 were excluded for HIV, and 14 for inadequate confirmation of PML. In the 35 remaining cases, survival for 1 year after PML diagnosis was reported in just three patients (9%). Diagnosis was made by brain biopsy (n=10),

autopsy (n=6), or MRI of brain AND positive JC virus PCR (n=19). Indications for R were lymphoproliferative disorder (n=33) and systemic lupus erythematosus (n=2). Median age was 63 years (range 30-89), with 19 female and 16 male patients. Seven cases were seen after SCT, 5 autologous and 2 allogeneic. In the 28 remaining patients, 10 had received purine analog therapy and 24 had received an alkylating agent in addition to R. T-cell studies were obtained at the time of PML diagnosis on 10 patients (Table).

Conclusion: Nine of 10 patients with complete T-cell studies had abnormal CD4/CD8 ratios (normal 0.9-2.7) or severe T-cell lymphopenia with CD4 count <100. This suggests that dysregulation of the cellular immune system may contribute to the development of PML after treatment with R and chemotherapy. Further study of T-cell changes associated with R administration would allow better understanding of the contribution of R to PML and other viral reactivation syndromes.

T-cell studies

Case	Transplant	Purine Analogue	Indication	CD4/CD8 Ratio	CD4+ (cells/ μ l)	CD8+ (cells/ μ l)	Survived
1	Auto	N	NHL	0.21	551	2596	Y
2	Auto	N	Follicular lymphoma	0.23	234	1015	N
3	-	N	DLBCL	0.3	540	1871	N
4	Allo	N	Hemolysis post- HSCT	0.31	1059	3453	Y
5	-	Y	CLL	0.34	2100	6200	N
6	-	N	MCL	0.35	110	310	N
7	-	N	DLBCL	0.39	94	243	N
8	-	N	CLL	0.92	287	311	Y
9	-	N	SLE	1.25	71	57	N
10	Auto	N	NHL	2.17	89	41	N

141 OBJECTIVE RESPONSES IN A PHASE I DOSE-ESCALATION STUDY OF SGN-35, A NOVEL ANTIBODY-DRUG CONJUGATE (ADC) TARGETING CD30, IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

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Background: CD30 expression by Reed-Sternberg cells is a defining feature of Hodgkin lymphoma (HL). The ADC SGN-35 comprises an anti-CD30 antibody conjugated to monomethyl auristatin E (MMAE). SGN-35 mechanism of action involves binding to CD30 on the tumor cell surface, ADC internalization, MMAE release and binding to tubulin, prompting cell cycle arrest and apoptosis.

Methods: A multicenter phase I dose escalation study was conducted in patients with refractory or recurrent CD30-positive hematologic malignancies. 29 patients (pts) were enrolled; 26 with HL, 3 with other CD30+ malignancies. Median age was 32 (range 22-87) and pts received a median of 5 prior therapies; 76% previously received an autologous stem cell transplant. SGN-35 dose levels were 0.1-2.7 mg/kg (2-hr outpatient IV infusion, premedications not required) every 3 weeks (wks).

Results: Dose-limiting toxicity was not defined; 1 infusion-related reaction was observed. One pt (0.1 mg/kg) experienced G3 hypercalcemia and 1 pt (1.8 mg/kg) had G4 thrombocytopenia (both reversible and possibly related). One pt (0.4 mg/kg) experienced a possibly related myocardial infarction that resolved without sequelae. The most common related adverse events were G1/2 fatigue, diarrhea and cough. Pharmacokinetic data indicate exposure (AUC) to SGN-35 increased relative to dose level, with no accumulation after repeated dosing. Best response: partial remission (n=9), stable disease (n=11), progressive disease (n=8), and not evaluable (n=1). At dose levels of ≥ 1.2 mg/kg, 7 of 13 pts (54%) achieved PR and remain on therapy at 11+ to 25+ wks; tumor reductions occurred in 11 of 13 pts. Enrollment continues at 2.7 mg/kg.

Conclusions: SGN-35, a novel ADC targeting CD30, was generally well tolerated at doses up to 2.7 mg/kg, and induced multiple objective responses in heavily pretreated pts. These encouraging results indicate SGN-35 should be further evaluated in phase II studies for pts with HL.

142 VACCINATION OF INDOLENT NON-HODGKIN LYMPHOMA PATIENTS WITH DENDRITIC CELLS LOADED WITH APOPTOTIC TUMOR CELLS INDUCES THE ACTIVATION OF NK CELLS AND THE DECREASE OF REGULATORY T CELLS IN PERIPHERAL BLOOD AND AT TUMOR SITE IN RESPONDING PATIENTS

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Introduction: To evaluate the safety and anti-tumor activity of a novel method of vaccination using dendritic cells (DCs) loaded with killed autologous tumor cells, 18 patients with measurable relapsed follicular (12) and lymphoplasmacytoid (6) non Hodgkin's lymphoma have been enrolled in a phase II study.

Methods: Each patient completed the four-cycle vaccination schedule receiving a SC injection of 50x10⁶ autologous DCs loaded with killed tumor cells at 2-week interval. Before, during and after vaccination, peripheral blood (PB) and lymph node (LN) samples were collected to assess specific antitumor immune responses and quantitative/qualitative changes of NK and regulatory T cells (Treg).

Results: Overall, vaccinations were well tolerated with no autoimmune reactions. With a median follow-up of 30.5 months (range 18-47 months), 6 of 18 had objective responses (33%). Three patients obtained complete remissions (CR). Three patients had partial responses (PR) lasting 7, 12 or 47 months. Twelve patients had stable (8) or progressive (4) disease. In PR patients, an increased frequency of T cells releasing IFN-γ in response to autologous tumor cells together with a shift towards effector memory stage were demonstrated in post-vaccine LN. In addition, in one out of the three CR patients it was possible to document a durable activation of tumor-specific anti-IgH-encoded peptide T cells in post-vaccine PB. Moreover, our DC-based vaccination promoted NK cell cytotoxic functions, since in responding patients' PB NK cells showed a shift towards the CD56dimCD16+ immunophenotype with a broad expression of NKG2D and NKp46 activation receptors. Finally, post-vaccine PB and LN of responding patients showed a strong reduction in CD4⁺CD25⁺FoxP3⁺ Treg.

Conclusions: Vaccination of NHL patients with autologous tumor-loaded DCs was well tolerated and induced durable clinical and immunological responses in patients with measurable disease.

143 A PHASE II TRIAL OF EXTENDED INDUCTION GALIXIMAB ([G] ANTI-CD80 MONOCLONAL ANTIBODY) PLUS RITUXIMAB[®] IN PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA (FL): INITIAL REPORT OF CALGB 50402

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Most B-NHL patients (pts) receive R, either as a single agent or in combination with chemotherapy. Numerous "biologic" agents are also being evaluated in combination with R to increase its activity. These combination regimens are an attempt to avoid non-specific chemo-associated toxicities while introducing alternative mechanisms-of-action (MOA) against drug-resistant cells. G is a primatized anti-CD80 monoclonal mAb with single-agent activity in psoriasis and previously treated FL; and, in combination with R, against relapsed FL. The CD80 molecule (i.e. B7.1) is found on the surface of activated macrophages, dendritic cells, and cells from various subtypes of NHL (e.g. FL). G's MOA include ADCC and possible immunomodulatory effects on host effector cells affecting the tumor microenvironment. Primary objectives of CALGB 50402 were to determine the ORR and TTP after upfront G+R. An ORR of 0.80 will be considered worthy of further investigation. G+R were given together weekly x 4; then every 2 months x 4 in pts with previously untreated CD20-positive FL pts: WHO grades 1-3a; bulky Stage II or III/IV; measurable disease; adequate hematologic, hepatic and renal function; signed IRB-approved informed consent. Sixty-two pts were registered; one pt withdrew consent prior to initiating therapy. Base-line characteristics of the 61 pts are: 61% M; 39% F; median age=57 yrs (range 22-85), with 48% of pts >60; 23% with an elevated LDH; FLIPI: good risk=20.3%; intermediate-risk=42%; high-risk=37%; histology=44% grade 1; 46% grade 2; 10% grade 3a. Current data are favorable, but marginally achieved the study goal with an initial response rate of 69% (41% CR; 28% PR), with a 95% CI of (0.56, 0.80). One pt withdrew consent at month 3 and was unevaluable for response. Median F/U time is 1.4 years (range 0.3-2 years) and the estimated 1-yr DFS probability is 0.87 (0.75, 0.93). Rx was very well tolerated, with only 13% experiencing grade 3 AEs. Further details, including delayed tumor responses, subset analysis regarding patient characteristics (e.g. FLIPI) vs. response to Rx, and a detailed toxicity profile will be presented at the meeting.

144 ACTIVITY OF VELTUZUMAB, A SECOND-GENERATION HUMANIZED ANTI-CD20 MAB, IN LABORATORY AND CLINICAL STUDIES

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Background: Veltuzumab (anti-CD20 hA20 MAb), in clinical trials for B-cell malignancies and autoimmune diseases, differs from chimeric rituximab by being humanized with completely different framework regions from epratuzumab (anti-CD22 MAb).

Methods: *In-vitro* comparisons to rituximab in human lymphoma cell lines involved binding, off-rates, lipid-raft trafficking, growth-inhibition, apoptosis, ADCC, and CDC. Therapy experiments utilized xenografted human lymphoma lines. B-cell depletion and PK were studied in Cynomolgus monkeys. In phase 1-2 clinical trials, patients (pts) with follicular (FL) or other NHL, predominantly stage III/IV, with 1-7 prior treatments (median, 2), received 80-750 mg/m² veltuzumab i.v. weekly x 4.

Results: Veltuzumab had similar binding, anti-proliferative, apoptotic, and ADCC effects *in-vitro*, but had significantly reduced off-rates (longer residence times) vs. rituximab for all lymphoma cell lines tested. *In-vivo* models showed antitumor effects of veltuzumab at single i.p. or s.c. doses as low as 0.05-0.1 µg. In NHL clinical studies, very low doses of veltuzumab depleted circulating B-cells after a single 80 mg/m² infusion, with durable complete responses of 28% (14/50) (median duration, 19.7 mo.) in FL pts for all doses. Also, 63% (5/8) of all NHL pts given only 80 mg/m² x 4 wks had an objective response, with 25% (2/8) being CR/CRu. Infusions at lower doses required 2 h for the first and 1 h for later infusions, with no toxicities beyond grade 1-2, or HAMA responses.

Conclusions: These results suggest that veltuzumab has differentiated efficacy and safety properties. The potency of a low-dose s.c. formulation in murine and monkey models, and low i.v.-doses in pts, justify ongoing clinical trials with s.c. veltuzumab.

145 LUMILIXIMAB IN COMBINATION WITH FCR FOR THE TREATMENT OF RELAPSED CHRONIC LYMPHOBLASTIC LEUKEMIA (CLL): RESULTS FROM A PHASE I/II MULTICENTER STUDY

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Lumiliximab is an anti-CD23 monoclonal antibody being investigated for relapsed CLL. In a previous study, lumiliximab monotherapy given weekly was well tolerated, achieved sustainable CD23 receptor occupancy and showed clinical activity. A Phase I/II, multicenter study was conducted to evaluate the safety & efficacy of lumiliximab in combination w/ fludarabine, cyclophosphamide, and rituximab (L+FCR) for pts w/ relapsed CLL. In addition, CD23 receptor occupancy on CLL cells and possible effects of elevated serum CD23 were evaluated. 31 pts received either 375 mg/m² (n=3) or 500 mg/m² (n=28) of L+FCR for up to six 28-day cycles. All pts completed treatment and follow-up is ongoing. A semi-quantitative flow cytometry method was used to measure CD23 receptor occupancy and serum CD23 was analyzed using an enzyme-linked immunosorbent assay. Median age at study entry: 58 yrs, Rai Stage I/II:71%, median # of prior regimens:2(1-10). Overall response rate was 65%: complete response (CR) 52% & partial response 13%. 5 of 8 pts w/ del (11q22.3) achieved CR. With median follow-up of 16.8 mos (1.5 -37.6), KM estimated median progression-free survival (PFS) for all pts was 19.3 mos. Median PFS for all responders and CR pts were 23.4 mos and 30.4 mos, respectively. 23 pts (74%) reported a Grade 3 or 4 event. Compared with published FCR data, L+FCR has a similar safety profile w/ no additional toxicities. L+FCR sustained CD23 receptor occupancy, not affected by elevated levels of serum CD23. L+FCR is an effective regimen for pts w/ relapsed CLL; producing an impressive CR rate, an encouraging PFS and a similar safety profile to that of FCR. A large, randomized, global study of L+FCR vs FCR (LUCID) is ongoing to further evaluate the safety & efficacy of this regimen.